EXHIBIT C

United States Patent [19]

Lowe, III et al.

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[54] **ARYL PIPERAZINYL-(C_2 OR C_4) ALKYLENE HETEROCYCLIC COMPOUNDS HAVING NEUROLEPTIC ACTIVITY**

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[52] **U.S. Cl.** **514/254**; 514/253; 544/230; 544/237; 544/284; 544/359; 544/363; 544/366; 544/367; 544/368; 544/372; 544/373

[58] **Field of Search** 544/368, 359, 363, 366, 544/367, 372, 373, 237, 284, 230, 368; 514/254, 253, 254

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,133,056	5/1964	Ash et al.	540/518
3,147,260	9/1964	Ash et al.	544/366
4,113,728	9/1978	Baggaley	544/368

FOREIGN PATENT DOCUMENTS

187322	7/1986	European Pat. Off.	544/362
8103493	12/1981	World Int. Prop. O.	544/322

OTHER PUBLICATIONS

Munson et al, Chem. Abst. vol. 98(1983) 143284e "4-amino-3-quinolinecarboxylic acids and esters as antisecretory anti-ulcer compounds".

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[57] **ABSTRACT**

Arylpiperazinyl-ethyl(or butyl)-heterocyclic compounds and their pharmaceutically acceptable acid addition salts are neuroleptic agents. They are useful in the treatment of psychotic disorders.

9 Claims, No Drawings

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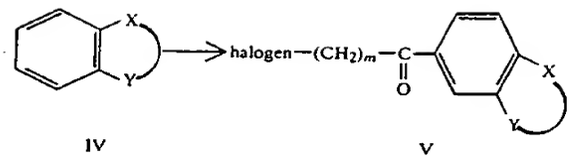

IV V

wherein X and Y are as defined above and m is 1 or 3. The compounds (V) are then reduced, e.g. with triethylsilane and trifluoroacetic acid in a nitrogen atmosphere, to form compounds (III).

When Ar is the oxide or dioxide of benzoisothiazolyl, the corresponding benzoisothiazolyl is oxidized under acid conditions at low temperatures. The acid used is advantageously a mixture of sulphuric acid and nitric acid.

The pharmaceutically acceptable acid addition salts of the compounds of formula I are prepared in a conventional manner by treating a solution or suspension of the free base (I) with about one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration and recrystallization techniques are employed in isolating the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic such as methanesulfonic, benzenesulfonic, and related acids.

The neuroleptic activity of the present compounds may be demonstrated by methods based on standard procedures. In one method, adult male Sprague-Dawley rats are pretreated with appropriate doses of the test compound by subcutaneous injection. One half hour later, all rats are injected intraperitoneally with 1 mg/kg apomorphine hydrochloride dissolved in an 0.1% ascorbate solution. The rats are rated behaviorally according to the following scale at 5, 15, 25, 35 and 45 minutes after the apomorphin injection: 0=alert but not moving, 1=moving about the cage, 2=discontinuous sniffing behavior, 3=continuous sniffing with discontinuous oral movements, and 4=continuous licking and chewing movements.

The neuroleptic activity of the compounds of this invention makes them useful for treating psychotic disorders in human subjects. For example, these compounds are useful for treating psychotic disorders of the schizophrenic types, and in particular the compounds are useful for removing or ameliorating such symptoms as anxiety, agitation, excessive aggression, tension, and social or emotional withdrawal in psychotic patients.

A neuroleptic compound of formula I, or a pharmaceutically-acceptable salt thereof, can be administered to a human subject either alone, or, preferably, in combination with pharmaceutically-acceptable carriers or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. A compound can be administered orally or parenterally. Parenteral administration includes especially intravenous and intramuscular administration. Additionally, in a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically-acceptable salt thereof, the weight ratio of active ingredient to carrier will normally be in the range from 1:6 to 2:1, and preferably 1:4 to 1:1. However, in any given case, the ratio chosen will depend on such factors as the solubility of the active component, the dosage contemplated and the precise route of administration.

For oral use of a neuroleptic agent of this invention, the compound can be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which can be used include lactose and corn starch, and lubricating agents, such as magnesium stearate, can be added. For oral administration in capsule form, useful diluents are lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient can be combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added. For intramuscular and intravenous use, sterile solutions of the active ingredient can be prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled to render the preparaton isotonic.

When a neuroleptic agent of this invention is to be used in a human subject to treat a psychotic disorder, the daily dosage will normally be determined by the prescribing physician. Moreover, the dosage will vary according to the age, weight and response of the individual patient as well as the severity of the patient's symptoms. However, in most instances, an effective amount for treating a psychotic disorder will be a daily dosage in the range from 5 to 500 mg, and preferably 50 to 100 mg, in single or divided doses, orally or parenterally. In some instances it may be necessary to use dosages outside these limits.

The following examples are provided solely for the purpose of further illustration.

EXAMPLE 1

6-(2-(4-(1-Naphthyl)piperazinyl)ethyl)-benzoxazolone

A. To a 500 ml three-necked round-bottomed flask equipped with mechanical stirrer and N_2 inlet were added 200 g of polyphosphoric acid, 13.51 g (0.1 mole) of benzoxazolone, and 13.89 g (0.1 mole) of bromoacetic acid. The reaction was heated with stirring at 115° C. for 2.5 hours and poured into 1 kg ice. The mixture was stirred mechanically for 1 hour to form a purple solid, which was then filtered off and washed with water. The solid was slurried with acetone for 30 minutes, a small amount of purple solid filtered off, and the brown filtrate evaporated. The resulting dark brown gum was slurried with 150 ml ethanol for 30 minutes, and the brown solid filtered off and washed with ethanol. This solid had a m.p. of 192°–194° C.

The solid (6.6 g, 0.0257 mole) was placed in a 100 ml three-necked round-bottomed flask equipped with magnetic stirrer, dropping funnel, thermometer, and nitrogen inlet and 19.15 ml (0.257 mole) of trifluoroacetic acid added. Triethylsilane (9.44 ml, 0.0591 mole) was added dropwise to the stirring slurry over 30 minutes. The reaction was stirred overnight at room temperature, then poured into 150 g ice. The mixture was stirred for 15 minutes, and the brown gum filtered off. The gum was dissolved in 100 ml ethyl acetate, and 125 ml cyclohexane added, giving a brown precipitate, which was filtered and washed with cyclohexane. The filtrate was evaporated and the resulting yellow solid slurried with 50 ml isopropyl ether. The pale yellow solid was filtered off and dried to give 2.7 g 6-(2-bromoethyl)-benzoxazolone (11% yield for two steps), m.p. 148°–151° C.

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EXAMPLE 6

6-(2-(4-(4-Methoxy-1-naphthyl)piperazinyl)ethyl)benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and N_2 inlet were added 0.24 g (1.0 mmol) of 6-bromoethylbenzoxazolone, 0.24 g (1.0 mmol) of 4-methoxy-1-piperazinylnaphthalene, 0.13 g (1.2 mmol) of sodium carbonate, and 25 ml of ethanol. The reaction was refluxed for 36 hours, cooled, diluted with water, and the product extracted into ethyl acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.49 g of a yellow oil. The oil was chromatographed on silica gel using chloroform as eluent to give 0.36 g of yellow crystals. The solid was dissolved in ethyl acetate, ethyl acetate saturated with HCl gas added, and the mixture concentrated to dryness to give 0.26 g (55%) of white salt crystals, m.p. 200° C. NMR (d, $CDCl_3$: 2.8–3.2 (m, 12H), 4.01 (s, 3H), 6.7–7.6 (m, 7H), 8.26 (m, 2H).

EXAMPLE 7

6-(2-(4-(5-Tetralinyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and N_2 inlet were added 1.0 g (3.9 mmol) of 6-bromoethylbenzoxazolone, 0.85 g (3.9 mmol) of 5-piperazinyltetralin, 0.4 g (3.9 mmol) of sodium carbonate, 2 mg of sodium iodide, and 30 ml of isopropanol. The reaction was refluxed for 18 hours, cooled, evaporated to dryness, and the residue dissolved in ethyl acetate/water. The pH was adjusted to 2.0 with 1N HCl, and the precipitate which had formed collected by filtration. The precipitate was suspended in ethyl acetate/water, the pH adjusted to 8.5 with 1N NaOH, and the ethyl acetate layer separated. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.7 g of a solid. The solid was dissolved in ethyl acetate, ethyl acetate saturated with HCl gas added, and the mixture concentrated to dryness to give 0.70 g (40%) of a yellow salt, m.p. 200° C. NMR (d, $CDCl_3$): 1.9 (m, 4H), 2.95 (m, 16H), 6.8–7.2 (m, 6H).

EXAMPLE 8

6-(2-(4-(6-Hydroxy-8-quinolyl)piperazinyl)ethyl)benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and N_2 inlet were added 0.84 g (3.5 mmol) of 6-bromoethylbenzoxazolone, 0.80 g (3.5 mmol) of 6-hydroxy-8-piperazinyl quinoline, 0.37 g (3.5 mmol) of sodium carbonate, 2 mg of sodium iodide, and 30 ml of isopropanol. The reaction was refluxed for 18 hours, cooled, evaporated, and the residue dissolved in ethyl acetate/water. The pH was adjusted to 2.0 with 1N HCl, and the phases separated. The aqueous phase was adjusted to pH 8.5 and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.33 g of a yellow solid. The solid was dissolved in ethyl acetate, ethyl acetate saturated with HCl gas added, and the mixture concentrated to dryness. The residue was crystallized from isopropanol to give 0.32 g (20%) of a yellow salt, m.p. 200° C. NMR (d, $CDCl_3$) 2.8 (m, 8H), 3.4 (m, 4H), 6.7–7.3 (m, 7H), 7.7–7.9 (m, 1H).

EXAMPLE 9

6-(2-(4-(1-(6-Fluoro)naphthyl)piperazinyl)ethyl)-benzoxazolone

A. To a 1 l round-bottomed flask equipped with condenser and N_2 inlet were added 345 ml (3.68 mol) of fluorobenzene and 48 g (0.428 mol) of furoic acid. To the stirring suspension was added in portions 120 g (0.899 mol) of aluminum chloride. The reaction was then stirred at 95° C. for 16 hours and then quenched by addition to ice/water/1N HCl. After stirring 1 hour, the aqueous layer was decanted off, and benzene and a saturated aqueous solution of sodium bicarbonate added. After stirring 1 hour, the layers were separated, the aqueous layer washed with benzene, acidified, and extracted into ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over sodium sulfate, and evaporated to a solid. The solid was triturated with isopropyl ether to give 5.0 g (6.1%) of white solid 6-fluoro-1-naphthoic acid, NMR (d, DMSO-d_6): 7.0–8.0 (m, 5H), 8.6 (m, 1H).

B. To a 125 ml round-bottomed flask equipped with condenser, addition funnel, and N_2 inlet were added 5.0 g (26.3 mmol) of 6-fluoro-1-naphthoic acid and 50 ml acetone. To the stirring suspension were added dropwise 6.25 ml (28.9 mmol) of diphenyl phosphoryl azide and 4 ml (28.9 mmol) of triethylamine. The reaction was refluxed 1 hour, poured into water/ethyl acetate, and filtered. The filtrate was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was further treated with HCl to form the hydrochloride salt and then liberated with sodium hydroxide to afford the free base 6-fluoro-1-amino-naphthalene as an oil, 1.0 g (24%).

C. To a 125 ml round-bottomed flask equipped with condenser and N_2 inlet were added 1.0 g (6.21) mmol) of 6-fluoro-1-amino naphthalene, 1.8 g (7.76 mmol) of N-benzyl bis(2-chloroethyl)amine hydrochloride, 3.3 ml (19.2 mmol) of diisopropylethylamine, and 50 ml isopropanol. The reaction was refluxed 24 hours, cooled, and evaporated to an oil. The oil was taken up in ethyl acetate, washed with water and brine, dried over sodium sulfate, and evaporated to an oil. The oil was chromatographed on silica gel using methylene chloride as eluent to afford 1.5 g (75.5%) of an oil, 1-benzyl-4-(6-fluoronaphthyl)-piperazine.

D. To a 125 ml round-bottomed flask equipped with N_2 inlet were added 1.5 g (4.69 mmol) of 1-benzyl4-(6-fluoronaphthyl)-piperazine, 1.2 ml (31.3 mmol) of formic acid, 3.0 g 5% palladium on carbon, and 50 ml ethanol. The reaction was stirred at room temperature for 16 hours, the catalyst filtered under N_2, and the solvent evaporated. The oil, N-(1-(6-fluoro)naphthyl)-piperazine (0.420 g, 39%), was used directly in the following step.

E. To a 100 ml round-bottomed flask equipped with magnetic stirrer, condenser, and N_2 inlet were added 0.420 g (1.83 mmol) of N-(1-naphthyl)piperazine, 0.440 g (1.83 mmol) of 6-(2-bromoethyl)-benzoxazolone, 194 mg (1.83 mmol) of sodium carbonate, 50 ml methylisobutylketone, and a catalytic amount of sodium iodide. The reaction was refluxed for 3 days, cooled, and evaporated to a brown gum. The gum was partitioned between 50 ml water and 75 ml ethyl acetate, the pH adjusted with aqueous 1N NaOH solution, the layers separated, and the ethyl acetate layer washed with water and brine. The ethyl acetate layer was dried over

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4-amino-2,1,3-benzothiadiazole, 2.54 g (13.2 mmol) mechlorethamine hydrochloride, 4.19 g (39.6 mmol) sodium carbonate, 2 mg sodium iodide, and 50 ml ethanol. The reaction was refluxed 2 days, cooled, and evaporated. The residue was taken up in methylene chloride, washed with water, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using ethyl acetate/methanol as eluent, and the product fractions collected and evaporated to an oil of 4-(2,1,3-benzothiadiazolyl)-N-methylpiperazine, 628 mg (20%). NMR (d, $CDCl_3$) 2.5 (s, 3H), 2.8 (m, 4H), 3.6 (m, 4H), 6.8 (m, 1H), 7.5 (m, 2H).

B. To a 25 ml round-bottomed flask equipped with condenser and N_2 inlet were added 620 mg (2.64 mmol) of 4-(2,1,3-benzothiadiazolyl)-N-methylpiperazine, 0.224 ml (2.64 mmol) vinyl chloroformate, and 15 ml dichloroethane. The reaction was refluxed 16 hours, cooled, and evaporated. The residue was chromatographed on silica gel using methylene chloride/ethyl acetate as eluent, and the product fractions collected to give yellow solid 4-(2,1,3-benzothiadiazolyl)-N-vinyloxycarbonylpiperazine, 530 mg (69%). NMR (d, $CDCl_3$): 3.6 (m, 4H), 3.8 (m, 4H), 4.4–5.0 (m, 2H), 6.6–7.6 (m, 4H).

C. To a 50 ml round-bottomed flask equipped with condenser and N_2 inlet were added 530 mg (1.83 mmol) 4-(2,1,3-benzothiadiazolyl)-N-vinyloxycarbonylpiperazine and 25 ml ethanol, and the suspension saturated with HCl gas. The reaction was refluxed 2.75 hours, cooled, and evaporated. The residue was triturated with acetone to give a yellow solid N-(2,1,3-benzothiadiazolyl)-piperazine, m.p. 240°–244° C., 365 mg (62%).

D. To a 125 ml round-bottomed flask equipped with condenser and N_2 inlet were added 365 mg (1.13 mmol) N-(2,1,3-benzothiadiazolyl)-piperazine, 275 mg (1.13 mmol) 6-(2-bromoethyl)benzoxazolone, 359 mg (3.39 mmol) sodium carbonate, 2 mg sodium iodide, and 40 ml ethanol. The reaction was heated at reflux for 2 days, cooled, and evaporated. The residue was taken up in methylene chloride, washed with water, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using ethyl acetate/methanol as eluent and the product fractions collected, dissolved in methylene chloride/methanol, precipitated by addition of an ethereal solution of HCl, and the solid filtered, washed with ether, and dried to give 228 mg (45%), m.p. 166°–170° C.

EXAMPLE 14

6-(2-(4-(1-Naphthyl)-piperazinyl)ethyl)benzothiazolone

To a 100 ml round-bottomed flask equipped with condenser and N_2 inlet were added 1.0 g (3.88 mmol) of 6-(2-bromoethyl)benzothiazolone, 822 mg (3.88 mmol) N-(1-naphthyl)piperazine, 410 mg (3.88 mmol) sodium carbonate, and 50 ml methylisobutylketone. The reaction was refluxed for 24 hours, cooled, and evaporated. The residue was taken up in ethyl acetate, washed with water and brine, dried over sodium sulfate, and evaporated. The resulting solid was treated with hot ethyl acetate to afford a white solid, m.p. 198°–220° C., 540 mg (36%).

EXAMPLE 15

6-(2-(4-(3-Benzoisothiazolyl)piperazinyl)ethyl)benzoxazolone

To a 125 ml round-bottomed flask equipped with condenser were added 4.82 g (0.022 mol) of N-(3benzoisothiazolyl)piperazine (prepared according to the procedure given in U.S. Pat. No. 4,411,901), 5.32 g (0.022 mol) of 6-(2-bromo)ethylbenzoxazolone, 2.33 g (0.022 mol) of sodium carbonate, and 50 ml of methyl isobutyl ketone. The mixture was refluxed for 18 hours. The reaction was cooled and partitioned between ethyl acetate and water. The ethyl acetate layer was isolated, washed with water and saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated to an oil. The oil was chromatographed on silica gel using ethyl acetate as eluent, and the product fractions collected and triturated with methylene chloride/isopropyl ether to give a white solid, 1 m.p. 185°–187° C. NMR ($CDCl_3$): 1.7 (bs,1H), 2.8 (m,8H), 3.6 (m,4H), 6.9–8.0 (m,7H).

EXAMPLE 16

5-(2-(4-(1,2-Benzisothiazol-3-yl)piperazinyl)ethyl)oxindole

To a 125 ml round-bottomed flask equipped with N_2 inlet and condenser were added 0.62 g (3.20 mmol) 5-(2-chloroethyl)-oxindole, 0.70 g (3.20 mmol) N-(1,2-benzisothiazol-3-yl)piperazine, 0.68 g (6.40 mmol) sodium carbonate, 2 mg sodium iodide, and 30 ml methylisobutyl ketone. The reaction was refluxed 40 hours, cooled, filtered, and evaporated. The residue was chromatographed on silica gel, eluting the byproducts with ethyl acetate (1 l) and the product with 4% methanol in ethyl acetate (1.5 l). The product fractions (R_f=0.2 in 5% methanol in ethyl acetate) were evaporated, taken up in methylene chloride, and precipitated by addition of ether saturated with HCl; the solid was filtered and washed with ether, dried, and washed with acetone. The latter was done by slurrying the solid with acetone and filtering. The title compound was obtained as a high melting, non-hygroscopic solid product, m.p. 288°–288.5° C., 0.78 g (59%).

In a manner analogous to that for preparing 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)oxindole, the following compounds were made:

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1-ethyloxindole hydrochloride, 25%, m.p. 278°–279° C.;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)1-methyloxindole hydrochloride hemihydrate, 42%, m.p. 283°–285° C.; MS(%): 392(1), 232(100), 177(31); Anal. for $C_{22}H_{24}N_4OS.HCl.\frac{1}{2}H_2O$: C 60.33, H 5.98, N 12.79. Found: C 60.37, H 5.84, N 12.77;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1-(3-chlorophenyl)oxindole hydrochloride hydrate, 8%, m.p. 221°–223° C.; MS(%): 488(1), 256(4), 232(100), 177(15); Anal. for $C_{27}H_{25}ClN_4OS.HCl.H_2O$: C 59.67, H 5.19, N 10.31. Found: C 59.95, H 5.01, N 10.14;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-3,3-dimethyloxindole hydrochloride hemihydrate, 40%, m.p. 289°–291° C.; MS(%): 406(1), 232(100), 177(42); Anal. for $C_{23}H_{26}N_4OS.HCl\frac{1}{2}H_2O$: C 61.11, H 6.24, 12.39. Found: C 61.44, H 6.22, N 12.01;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1,3-dimethyloxindole, 76%, m.p. 256° C.;

5'-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-spiro[cyclopentane-1,3'-indoline]-2'-one hydrochloride hemihydrate, 50%, m.p. 291°–293° C. (dec.); MS(%): 432(1), 232(100), 200(11), 177(36); Anal. for $C_{25}H_{28}N_4OS.HCl.\frac{1}{4}H_2O$: C 62.81, H 6.33, N 11.72. Found: C 63.01, H 6.32, N 11.34;

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5-(2-chloroethyl)-6-fluorooxindole, 62%, m.p.188°–190° C.; NMR(DMSO-d_6) 3.05(t,2H), 3.5(2,2H), 3.85(t,2H), 6.6–7.3(m,2H);

5-(2-chloroethyl)-7-fluorooxindole, 79%, m.p.176°–179° C.; MS(%); 213(50), 180(20), 164(100), (76);

5-(2-chloroethyl)-6-chlorooxindole, 94%, m.p.210°–211° C.;

5-(2-chloroethyl)-3,3-dimethyl-6-fluorooxindole ($C_{12}H_{13}ClFNO$, 84%, m.p.195°–198° C., NMR(DMSO-d_6) 1.3(s,6H), 3.05(t,2H), 3.7(t,2H), 6.65(d,1H), 7.1(d,1H), 10.1(br s,1H);

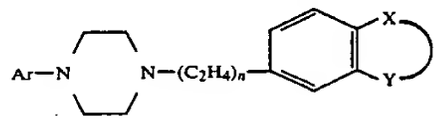
5-(4-chlorobutyl)oxindole, 40%, oil, NMR($CDCl_3$): 1.6–2.0(m,4H), 2.6(m,2H), 3.6(m,4H), 6.8–7.15(m,3H), 9.05(br s,1H);

5-(4-chlorobutyl)-1-ethyloxindole, 48%, oil, NMR($CDCl_3$): 1.25(t,3H), 1.5–1.95(m,4H), 2.6(m,2H), 3.5(s,2H), 3.55(t,2H), 3.75(q,2H), 6.7–7.2(m,3H); and

5-(4-chlorobutyl)-7-fluorooxindole, 71%, m.p.168°–173° C.

We claim:

1. A compound of the formula



or a pharmaceutically acceptable acid addition salt thereof, wherein

Ar is benzoisothiazolyl or an oxide or dioxide thereof each optionally substituted by one fluoro, chloro, trifluoromethyl, methoxy, cyano, or nitro;

n is 1 or 2; and

X and Y together with the phenyl to which they are attached form benzothiazolyl; 2-aminobenzothiazolyl; benzoisothiazolyl; indazolyl; 2-hydroxyindazolyl; indolyl; oxindolyl optionally substituted by one to three of (C_1–C_3)alkyl, or one of chloro, fluoro or phenyl, said phenyl optionally substituted by one chloro or fluoro; benzoxazolyl; 2-aminobenzoxazolyl; benzoxazolonyl; 2-aminobenzoxazolinyl; benzothiazolonyl; bezoimidazolonyl; or benzotriazolyl.

2. A compound aceording to claim 1 wherein X and Y together with the phenyl to which they are attached form benzoxazolonyl.

3. A compound according to claim 2 wherein Ar is benzoisothiazolyl and n is 1.

4. A compound according to claim 1 wherein X and Y together with the phenyl to which they are attached form oxindole.

5. A pharmaceutical composition having neuroleptic activity comprising a compound according to claim 1 in an amount effective in the treatment of neuroleptic diseases, and a pharmaceutically acceptable carrier.

6. A composition according to claim 5 wherein X and Y together with the phenyl to which they are attached form benzoxazolonyl.

7. A composition according to claim 6 wherein Ar is benzoisothiazolyl and n is 1.

8. A composition according to claim 5 wherein X and Y together with the phenyl to which they are attached form oxindole.

9. A method of treating neuroleptic diseases which comprises administering to a subject in need of treatment a neuroleptic amount of a compound according to claim 1.

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